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Tissue Factor – A Receptor Involved in the Control of Cellular Properties, Including Angiogenesis

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Summary

Tissue factor (TF), the major initiator of blood coagulation, serves as a regulator of angiogenesis, tumor growth and metastasis. In several models, TF expression mediates upregulation of the proangiogenic vascular endothelial growth factor (VEGF) that can directly act on endothelial cells to promote vessel formation. This occurs through ligand binding, activation of signaling cascades, signal transduction and alteration of growth factor expression and is mediated by both, coagulation-dependent and -independent pathways. Depending on the cell type and the biological settings, TF seems to affect cellular properties through (i) factor VIIa (FVIIa)-dependent proteolysis of factor Xa (FXa) and thrombin and subsequent activation of proteinase activated receptor (PAR) -1 and PAR-2, (ii) through direct FVIIa signaling and mitogen activated protein (MAP) kinase activation, that is conferred by a not yet identified receptor, (iii) through interaction of FVII(a) proteolytic activity and signaling of the cytoplasmic domain and (iv) through cytoplasmic signaling independent of ligand binding. The role of phosphorylation of the cytoplasmic domain and the pathways controlling phosphorylation of TF remain poorly understood.

Introduction

Tissue factor, a 47 kD membrane-located glycoprotein (1-7), is the primary initiator of coagulation, which serves as a cell-surface receptor and non-enzymatic cofactor for plasma FVII(a) (2-4). Endothelial cells and monocytes lack detectable TF expression under physiological conditions, while extravascular cells in the subendothelial layer of the vessel wall show constitutive TF expression, forming a hemostatic "envelope" (5-8) ready to activate coagulation whenever vascular integrity has to be restored (9-11).

In the last years, however, it became evident that TF has additional biological functions apart from hemostasis. One of the first indications for a non-hemostatic function was the characterization of TF as an immediate early gene that is induced during cell division (12, 13) and upregulated during monocytic differentiation (14, 15). As an immediate early gene, TF is rapidly induced in response to pathophysiologically relevant stimuli such as cytokines (16-26), growth factors (27, 28) including VEGF (29), endotoxin (20, 28-38), advanced glycation endproducts (AGEs) (39, 40), LDL (41, 42), and hypoxic conditions (43-46) in a variety of cells, including endothelial cells and monocytes. TF expression itself is under cell-type specific control through different transcriptional pathways. The transcription factor Sp1 maintains basal constitutive TF expression (47, 48). Inducible TF expression can be explained either by loss of down-regulating activities (49, 50) or by induction of different transactivating transcription factors, such as members of the nuclear factor-kappa B (NF-κB)- (25, 26, 32, 38, 51-62) and activated protein (AP)-1/β-Zip-families (25, 57, 60), early growth response (Egr)-1 (40, 63-65) and Sp1 (40, 59, 65, 66). VEGF induced endothelial TF expression greatly differs from that of inflammatory stimuli because it is mediated by Egr-1 (64, 67) and is due to the activation of nuclear factor of activated T cells (NFAT) (68). The presence of different pathways is also reflected by different activation patterns in response to different stimuli (69). Furthermore, this complexity is increased by the observation that the stability of TF can be modulated. In interleukin (IL)-1 stimulated endothelial cells, the half life of TF is reduced in the presence of FVII(a) (70), an example of a cell biological function of the TF-FVII(a) interaction.

Results from knock-out animals, malignant and non-malignant cells have suggested that TF and its ligand, FVII(a), indeed have functions compatible with its regulation as an immediate early gene in addition to the activation of coagulation. *In vitro* studies, in which TF-FVIIa interactions induce phosphatidylinositol-specific phospholipase C-mediated Ca^{2+} signaling (71, 72) supports the idea that TF functions as a true receptor, although it is not yet known, whether TF exhibits signal transduction activity *in vivo*. Thus, TF might not only function as initiator of coagulation but also as a receptor controlling cellular properties and responding to environmental stimuli, such as hypoxia, inflammation and tumor growth. This is supported by the structural homology of TF to the members of the class II cytokine receptor family (73). This review will summarize some of these results.

TF and VEGF are Regulated by Overlapping Pathways

TF is an immediate early gene whose transcription is immediately activated when cells start to grow (12, 13). Thus, some transcription

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Table 1 Examples of transcription factors inducing TF and VEGF transcription

Transcription factors	TF		VEGF	
	Cell lines	References	Cell lines	References
Up1	Endometrial stromal cells Smooth muscle cells	86 41	Endothelial cells Cardiac myocytes Fibroblasts Carcinoma Glioma cells	82 83 84, 85 74, 88 87
AP-1	Monocytes Endothelial cells Fibroblast Lung of trauma rats	30, 53, 89 26, 57, 58 59, 68, 77, 78 49, 61 62	Pulp cells Osteoblastic cells Keratinocytes Astrocytes Glioma cells Glioblastoma cells	88 89 90 91 87, 91 93
NF-kappaB	Monocytes Endothelial cells Lung of trauma rats	38, 53, 64, 89 25, 26, 58 67, 68, 77-81 82	Osteoblastic cells Skin-derived cells	89 94

factors regulating TF also induce VEGF transcription, essential for tumor growth and wound healing (49, 63, 74-76). Simultaneous activation of TF and VEGF transcription may occur because some transcription factors are involved in the regulation of both (74-94) (Table 1). Furthermore, the TF-FVIIa complex induces members of the AP-1 family, which in turn can activate TF and VEGF transcription (95). Based on these observations, it is explained why TF and VEGF are co-expressed under similar conditions (96) and in some tumors (97).

Biological Phenomena under Control of Tissue Factor

Embryogenesis

Since no human disease has been attributed to a deficiency of TF, it has been speculated that the complete loss of TF is incompatible with life. Some studies have shown the crucial role of TF in embryonic development, and have looked at the cellular distribution of TF during embryogenesis (98). At early stages of murine (6.5 and 7.5 pc) and human (stage 5) embryonic development, there is a strong expression of TF in both ectodermal and endodermal cells particularly in epithelial areas with high levels of morphogenetic activity. While FVII antigen could not be detected during early embryogenesis (97), the presence of FVII transcripts at day 7.5 implicates that small amounts of FVII might already be available to bind to TF (99). The role of TF as a morphogenetic factor was further supported by several studies, demonstrating that targeted disruption of the TF gene in mice results in embryonic lethality (100-102). The embryonic phenotype was characterized by an increased fragility of the endothelial cell-lined channels in the yolk sac, which ruptured when blood pressure increased around day 9 of gestation. Formation of microaneurysms and blood lakes resulted in abnormal vitelloembryonic circulation, extensive hemorrhages into the yolk sac, loss of integrity in extra-embryonic tissues and subsequent embryonic death (102). Lethality of TF(-/-) mice, thereby, substantially differs from the bleeding phenotype observed in fibrinogen deficient mice (103) thus suggesting a hemostasis-independent role of TF during embryogenesis, which is further supported by other studies (104, 105). Since abnormal yolk sac vasculature resembles in part the phenotype found in VEGF-deficient embryos (106, 107), it has been suggested that the functions of VEGF and TF might be interrelated (96). In one study with TF (-/-) embryos, a low percentage of the TF-deficient embryos escaped embryonic lethality and survived to birth, yet dying shortly after due to lethal hemorrhage (102). This shows that genetic compensation can occur and adjust TF deficiency for a limited period of time. Compensation can also be conferred by a human TF minigene which can rescue murine TF(-/-) embryos from embryonic lethality (104). The requirement of TF to maintain the structure of the placental labyrinth and uterine hemostasis (108) might also be related to its proposed non-hemostatic functions such as regulation of protease generation, initiation of FVIIa-dependent cellular signaling (109) and modulation of cellular adhesion (110, 111).

TF as a Trigger of Growth Factor Production and Wound Healing

Induction of TF by cytokines, growth factors (including VEGF) and platelet or tumor derived products (29, 68, 112-114) results in the production of fibrin and sequential activation of tissue plasminogen activator (tPA) and plasmin, which promote the degradation of matrix proteins. This is a vital step for the migration and sprouting of tumor cells and endothelial cells during angiogenesis (115-117), tumor growth, metastasis and wound healing (118). This raised the question of whether TF participates via proteases generated downstream, or more directly. The interaction of FVII(a) with TF induces transcription and expression of growth factors such as amphiregulin, heparin-binding epidermal growth factor (EGF), connective tissue growth factor (CTGF) and fibroblast growth factor (FGF)-5, as well as proinflammatory cytokines (IL-1beta, IL-8, leukemia inhibitory factor (LIF), and macrophage inflammatory protein (MIP) 2 alpha), transcription factors (c-fos, egr-1, and myc) and genes involved in cellular reorganisation and migration such as urokinase-type plasminogen activator receptor (uPAR) and collagenases 1 and 3 in human keratinocytes (95), and Cyr61 and CTGF in fibroblasts (119). All of these genes are related to wound healing (118). A cycle exists with respect to TF and VEGF, since each can induce the other (29, 120-123). The pattern of genes induced in keratinocytes and fibroblasts further supports that the TF-FVII(a) complex may play an active role in early wound repair (95). A recent study showed the interplay of growth factors, coagulation factors, and cell migration during wound healing in a wound model of cultured endothelial cells (124). Cells away from the wound internalize VEGF via receptor-mediated endocytosis and transport VEGF to endosomal compartments; cells at the edge of the wound rapidly translocate VEGF to the nucleus. In the latter, levels of wound healing related proteins such as factor VIII, TF and tPA rapidly and dramatically increase (125). Thus, the common pathway of regulation of VEGF and TF is supplemented by common growth factors controlled by or controlling TF and VEGF.

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Vasculogenesis, wound healing, tumor growth and metastasis do not only require a coordinate regulation of cell growth and matrix processing, they also require cell migration (115). If, under some circumstances, TF would play a role as suggested above, one would expect to find situations and mechanisms in which TF and migration are coupled. Consistently, the TF-FVIIa complex has been demonstrated to exhibit a chemotactic migration activity for smooth muscle cells (126) and pancreatic cancer cells (127), hence mimicking the effect of platelet-derived growth factor (PDGF)-BB and bFGF (126). Incubation of fibroblasts with FVII(a) also reduces the PDGF concentration required to stimulate fibroblast migration by 100-fold (128). Furthermore, a recent study demonstrates that TF-dependent migration of rat smooth muscle cells can occur independently of FVIIa (129). Since vitelline vessels from TF(–/–) mice were deficient in smooth muscle α-actin expressing mesenchymal cells, it is supposed that TF is crucial for smooth muscle cell (SMC) recruitment (96). Furthermore, TF mediates the crossing of mononuclear phagocytes through endothelium in the basal-to-apical direction (reverse transmigration), which resembles migration across vascular and lymphatic endothelium during atherosclerosis and resolution of inflammation, respectively (111). Migration and polarization involve changes in the cytoskeleton. Both intracellular signaling and extracellular interactions can induce cell migration. TF distribution on polarized cells significantly differs from cells with less polar morphologies (130-133) and cytoskeletal-disrupting agents reduce TF expression (134). A molecular pathway by which TF might support cell migration and cellular trafficking is the binding of actin-binding protein (ABP)-280 filamin-1 to the cytoplasmic domain of TF. Recruitment of ABP-280 results in the reorganization of actin filaments, cell spreading and migration (110). These effects are mediated by interactions of the TF cytoplasmic tail with cytoskeletal adaptor proteins (110), and thus might explain the functional significance of the TF cytoplasmic domain in metastasis and vasculogenesis (109, 135-137). It is unknown whether phosphorylation of TF plays a role for interaction with ABP-280. Furthermore, the association of TF with elements of the cytoskeleton is observed in dynamic membrane regions of spreading cells and the motility of these cells can be increased by incubation with FVII(a) (132). Although the exact structural components for TF-dependent induction of migration and its *in vivo* consequences remain unknown, there are several situations where this property may be operative. These include: (i) during wound healing and in arteriosclerotic plaques in which TF-rich regions are also those showing an increase in smooth muscle cells, (ii) in embryogenesis, where TF(–/–) mouse embryos show reduced recruitment of smooth muscle actin positive cells, and (iii) in solid tumors, where tumoral TF could participate in angiogenesis, tumor growth and metastasis.

TF and Tumor Growth

TF is expressed on the cell surface of a variety of solid tumors, particularly those of epithelial origin (97, 138-140). In many tumors, TF expression correlates with the histologic grade of malignancy (141-144), tumor invasiveness (145), multi-drug resistance (146) and prognosis (147, 148). However, in some tumors, such as glioma (149) and breast cancer, contradictory results have been described (150). Several studies demonstrate that recruitment and/or activation of TF-expressing stromal cells is indicative of a progression to invasive breast cancer (151). Consistently, TF has been localized to vascular endothelial cells and tumor cells within the tumors of invasive breast cancer but not in fibrocystic disease of the breast (152). In contrast, others have reported little obvious correlation with malignant progression from in situ lesions to invasive cancer even though epithelial cells exhibited TF immunoreactivity (151). This is in accordance with the observation that proliferative and differentiation processes in the mammary gland are associated with enhanced TF expression even in the absence of malignancy (144). Therefore, one may speculate that cofactors are needed to turn physiological TF expression into a tumor growth promoting event. For instance, glioma cells generate thrombin in the presence of coagulation factors; thrombin then induces glioma cell proliferation *in vitro*, while TF on its own has no proliferative effect (149). The failure to establish a correlation of TF with the proliferative activity or the invasive character of human pituitary adenomas (153) and the observation that TF(+/+), TF(+/–), and TF(–/–) teratomas and teratocarcinomas are indistinguishable with regard to growth *in vitro* (154) further implies that expression of TF and the cellular phenotypes associated with TF reflect the differences in nature of various native tumors. TF, however, is associated with enhanced *in vivo* growth of a variety of primary tumors cells such as human pancreatic carcinoma (145) and human melanoma (122) cell lines. The finding that alterations of TF levels do not affect the proliferation of Meth-A sarcoma cells *in vitro*, but effectively induce Meth-A sarcoma growth *in vivo* (122) indicates that TF is involved in tumor growth at least in some tumors via its effects on angiogenesis. The capacity of TF to initiate fibrin formation resulting in plasminogen activation may further contribute to its reported effects on angiogenesis and tumor invasiveness (96, 155).

TF and Angiogenesis

Many tumors, especially those of epithelial origin, arise as avascular masses and vascularization is required for further growth and survival (156). Clinical data suggest a relation between TF and tumor angiogenesis. The most direct evidence comes from the correlation of TF expression with the microvessel density, which is an established marker for tumor angiogenesis (120, 143, 148). A correlation between TF and VEGF has been described in various human tumors (97, 120, 152). A significant relationship between TF expression and the expression of VEGF was discovered in patients with non-small-cell lung carcinoma and is supposed to serve as prognostic and predictive factor (148). Furthermore, TF and VEGF have been co-localized in vascular endothelial cells and tumor cells from patients with breast cancer, thereby supporting the hypothesis that tumor cells and nearby endothelial cells might interact in regulating vessel formation (97, 152).

The observation that TF is an immediate early gene activated when cells start to divide (12) was at first in contrast to the finding that TF expression does not control Meth-A sarcoma cell proliferation *in vitro* (122). When Meth-A sarcoma cells were stably-transfected with TF plasmids in the sense or antisense orientation, or with vector alone, cell growth rates of all cell lines were identical (120). However, when these Meth-A sarcoma transfectants were implanted into C3H-mice, tumor cells that overexpress sense TF grew more rapidly (122). The difference between sense and vector transfected tumors was statistically significant eight days after implantation. Consistent with a role of TF in promoting tumor growth, the growth of tumors expressing TF in the antisense orientation was remarkably reduced and significantly differed from TF sense tumors already at day four. Since this effect could not be explained by an increase in proliferation, it was suggested that TF may regulate angiogenic properties of tumors. This hypothesis was based on several observations. Firstly, the vascularization evaluated by vessel density and blood flow was greatly enhanced in sense-TF transfected

Fig. 1 The role of TF in tumor vascularization. The vessels growing towards the implanted tumor lines were visualized on day 6 by Indian ink. Abbreviations, v: vector, s: sense TF, as: antisense TF, ts: truncated TF. Magnification is ×9

tumors but significantly reduced in antisense transfectants when compared to vector-transfected control cells (Fig. 1). Secondly, VEGF mRNA and protein were upregulated in almost all TF overexpressing cells *in vitro* and *in vivo*, although some cells failed to demonstrate increased VEGF production (121, 122). Finally, large blood vessels demonstrated a remarkable smooth muscle α-actin positivity (P. Nawroth, unpublished observation), indicative of an increased recruitment of smooth muscle α-actin expressing mesenchymal cells that participate in the organization of the vessel wall. Beside their angiogenic activities, Meth-A sarcoma cells overexpressing TF suppressed the anti-angiogenic molecule thrombospondin, this therefore shifted the tumor tissue unidirectionally towards vessel formation (122). The role of TF in tumor angiogenesis, however, is still controversial. While some investigators have reported a significant correlation between TF and VEGF in human melanoma cell lines (121), others have demonstrated that increased TF expression does not lead to increased VEGF expression in human melanoma cells (135, 154). These contradictory results are, at least in part, explained by differences in the methods used. Abe and colleagues used preparations of human melanoma cells, previously characterized as high TF- and high VEGF-producers or as low TF- and low VEGF- producers, respectively. When these cell lines were inoculated into severe combined immunodeficient (SCID) mice, the high TF-producing cell lines generated highly vascularized solid tumors, while low-producers formed relatively avascular tumors. This indicates that the correlation between TF and VEGF is also seen *in vivo*. Upon transfection with TF overexpressing plasmids, the low TF/low VEGF-producing cells were turned into high producers of both TF and VEGF (121). This indicates that TF might directly affect VEGF expression. To define the structural requirements for this upregulation, TF-plasmids containing a procoagulant defective extracellular domain or TF-plasmids with a cytoplasmic deletion were transfected. Cells expressing procoagulant deficient TF induced VEGF in the same range as cells overexpressing full length TF. In contrast, transfectants with the cytoplasmic tail deletion, demonstrated a significantly reduced VEGF expression, but no reduction in TF expression. This indicates that the cytoplasmic domain is required for VEGF expression (see below). Bromberg and coworkers performed similar studies, but used low TF-producers that were not characterized by their endogenous VEGF expression capacity. When these cells were engineered to overexpress TF, no effect on VEGF expression and vascularisation was detected *in vitro* and *in vivo* (135). In addition, the increased metastatic potential observed in TF-overexpressing cells was dependent on both the extracellular and the cytoplasmic domain (135). This implies that the genetic background of the melanoma cell lines may determine whether TF-dependent or -independent angiogenesis occurs. In this context, we have observed that not all tumor cells which are derived from the same parental cell in single cell colonies respond to the overexpression of TF by inducing VEGF (P. Nawroth, unpublished observation). This in turn implies that the switch of tumor cells to be responsive to a TF mediated VEGF induction may be controlled by the same mechanisms that switch a tumor to an angiogenic phenotype. Therefore TF plays a role in tumor angiogenesis at least in some tumors, but it is definitely not the only player that contributes to vessel formation. Consistently, in those tumor cells that are incapable of expressing TF, VEGF transcription was not completely abolished (122). The recent observation that tumor growth, tumor frequency and tumor vascularity of teratoma and teratocarcinoma cells lacking TF do not differ from these observed in cells that express TF supports that additional factors are operative in angiogenesis and tumor vascularization (154) and is consistent with the clinical observation that some (120, 148) but not all tumors (147) show co-localization of TF and VEGF. This is further strengthened by the finding that embryonic lethality due to defective vessel formation can be compensated in a small number of TF(-/-) mice (102, 154). A further level of complexity is reached by the fact that possible mechanisms by which TF induces tumor-associated angiogenesis via VEGF are thought to be controlled through FVII(a)-dependent and independent pathways. Remarkably, activation of coagulation itself can also result in the induction of VEGF. Platelets are a rich source of VEGF, which is released by agonists such as thrombin (157), and thus contributes to the recently described proangiogenic activity of thrombin (158). TF-dependent release of VEGF, in turn, induces platelet adhesion to endothelial cells (157). Thus, tumor cells might ensure their own blood supply through TF-dependent thrombin generation, local platelet activation, release of VEGF and resultant angiogenesis (145). Furthermore, VEGF stimulates EC to induce (39) and expose TF (120) and thus promotes thrombin generation. Thrombin forms an extracellular

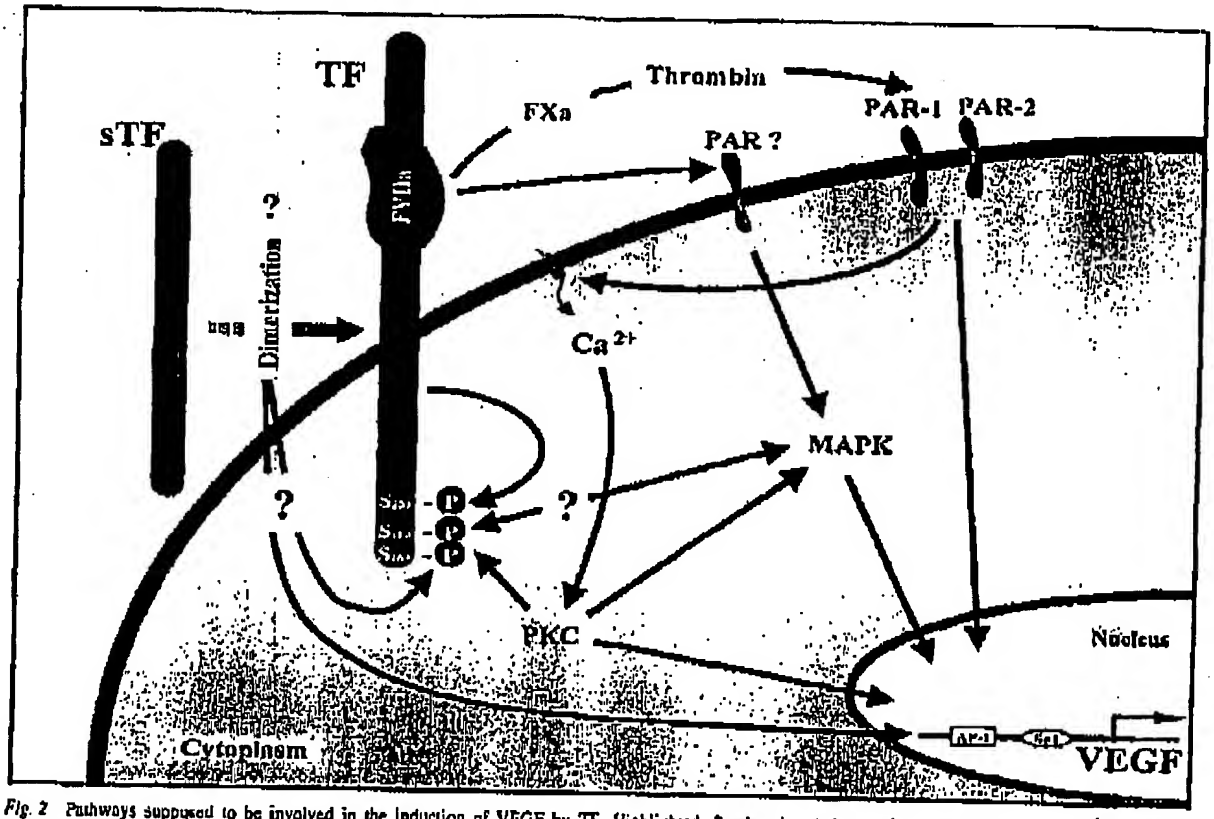

Fig. 2 Pathways supposed to be involved in the induction of VEGF by TF. Highlighted. P: phosphorylation, Ca^{2+}: calcium, S_{253}, S_{258}, and S_{263}: serine residues of mature human TF protein numbered according to Genebank (accession N°. AAA61153). Abbreviations. TF: tissue factor, sTF: soluble tissue factor, FXa: factor Xa, VEGF: vascular endothelial growth factor, MAPK: mitogen activated protein kinase, PKC: protein kinase C, PAR: protease-activated receptor

fibrin barrier, destroys the basal membranes by activating progelatinase-A and thus allows proliferation of ECs into the new tumoral fibrin matrix (159). Thrombin-dependent induction of endothelial cell proliferation potentiates this effect. Thus, there are several pathways linking TF and TF-initiated activation of coagulation to angiogenesis.

TF as a Component Involved in Metastasis

In general, TF expression is more commonly observed in metastatic tumors (which are frequently also more angiogenic) than in primary cancer (160). This has been demonstrated in patients with metastatic colorectal tumors (147, 160), non-small-cell lung carcinoma (161) and breast cancer (162). The outcome in the TF-positive groups was significantly worse than that in TF-negative groups. Consistently, treatment of mice with the thrombin inhibitor hirudin reduces pulmonary tumor seeding after tail vein injection of melanoma cells (163). Similarly, blocking coagulation at the level of TF, FXa or thrombin inhibited hematogenous metastasis in SCID mice (164). Therefore, the role of procoagulant activity in the metastatic function of TF was examined in genetically engineered cells expressing defined amounts of TF. A mutant form of TF, partially defective in procoagulant activity demonstrated the same metastatic effect as normal TF in melanoma cells, and initially implied that TF procoagulant activity might not be involved (165). However, mutation of the FVII-binding sites, which subsequently preventing TF-FVIIa complex formation, significantly reduced metastasis in a human melanoma cell line and clearly demonstrated that procoagulant activity of TF is involved in metastasis (135, 136).

TF and the Integrity of the Vascular Wall

TF plays an important role in the maintenance of the integrity of the vascular wall (9). Under physiological conditions, endothelial cells do not express TF (5, 22, 134), while TF is induced by TNFα in endothelial cells lining the tumor vasculature and has been demonstrated to play a role in thrombosis mediated tumor necrosis through directly blocking blood supply by fibrin generation (22, 29, 166-169). Furthermore, TF(-/-)-mice, that died between E8.5 and 10.5, exhibited a lack of normal interaction between peri-endothelial and endothelial cells, especially in the yolk sac vasculature (100). This defect in heterotypic vascular cell-to-cell interactions resulted in the fusion of capillary lumens and formation of a single, large lagune (100) and supports the important role for TF in developing and/or maintaining vascular integrity. Both apoptosis and TF de-encryption are associated with cell membrane alterations (170-173) and conditions that resulted in endothelial and fibroblast apoptosis were associated with de-encryption of TF activity (171, 174). Thus, TF controls the integrity of the vascular wall in embryogenesis, probably by orchestrating the recruitment of the

endothelial lining cells and by regulating of blood flow. Future studies will show the mechanisms linking apoptosis to TF.

Mechanisms by which TF Affects Cellular Functions

The mechanisms by which TF participates in angiogenesis, vasculogenesis and tumor growth and invasion are not yet fully understood. However, it appears that extra- and intracellular pathways are involved, which can be dependent or independent of FVII(a) ligation. The diversity of pathways identified to date illustrates the complexity of TF signaling, which, in addition, is dependent on the cell types (Fig. 2).

TF-dependent Functions with FVIIa-dependent Activation of Coagulation

Recent studies demonstrate that TF is involved in VEGF expression in fibroblasts which is dependent on FVII(a) binding and the activation of FXa and thrombin (175, 176). Consistently, recombinant FVIIa failed to induce VEGF expression in the absence of FX, while purified FXa, thrombin or PAR-1 induced VEGF expression (176). Thrombin and FXa also induced MAP kinase activation, while FVIIa did not in this model (176). Since TF/FVIIa induced MAP kinase activation was also present when cells were transfected with a cytoplasmic domain deleted mutant, direct FVIIa signaling via the cytoplasmic domain could be excluded and suggests the involvement of PARs in cellular signaling (176). This correlates with the recent observation that in the presence of TF and FXa, picomolar concentrations of FVIIa are sufficient to activate PAR-2 and, to a lesser extent, PAR-1 in endothelial cells, fibroblasts and keratinocytes (177). In the presence of high amounts of TF, TF-FVIIa protease signaling further results in direct activation of PAR-2 that is independent of FXa or FIIa and thereby contributes to endothelial cell activation.(177). This sheds light on the experimental approaches by which cells are engineered to overexpress TF, as these conditions may activate signal transduction pathways that do not occur under physiological settings. It is unknown whether FVII(a) and/or its proteolytic activity is required for embryogenesis, since at very early stages TF is expressed, but FVII-antigen is not detectable (98). A recent study, however, demonstrates the presence of FVII transcripts during early embryogenesis, implying that small amounts of FVII might be available to bind to TF (99). In addition, low levels of maternal FVII might also be activated by embryonic TF (105). Looking at the structural components of TF involved by investigating mutant hTF minigene rescued mTF(-/-) mice, it became evident that the extracellular domain of TF, but not its cytoplasmic tail was indispensable for survival (105). Due to similarities in the lethality of TF (-/-), prothrombin (-/-) and PAR-1 (-/-) mice, it is speculated that TF may function in embryogenesis through generation of thrombin and subsequent activation of PAR-1 dependent intracellular signaling into the yolk sac (105). Taken together, these data suggest that VEGF expression is regulated through FXa and thrombin via PAR-1 and possibly PAR-2.

TF-dependent Signaling with FVIIa Protease Activity

Consistent with the characterization of TF as a member of the class II cytokine receptor superfamily, direct intracellular signaling (independent of downstream formation of other proteases) in cells exposed to FVIIa has been reported in a variety of TF expressing cell lines (endothelial cells, baby hamster kidney (BHK) cells, the human bladder carcinoma cell line J82, keratinocytes, monkey kidney fibroblasts) (71, 178). Binding of FVIIa to cell surface-associated TF results in the production of intracellular signals through cytosolic calcium alteration (71), transient tyrosine phosphorylation (179), MAP kinase activation (178, 180) and gene transcription (58, 95). The mechanism for TF-FVIIa induced signal transduction across the membrane is not yet known. Several studies have demonstrated that the signal transduction pathways induced by FVIIa differ from those induced by trypsin, thrombin or FXa (71, 175-177, 181-183). The proteolytic activity of cell-bound FVIIa is required to induce intracellular activity, but FVIIa-bound TF is not subject to proteolysis (182). In BHK, CHO and MDCK cells, FVIIa-dependent cellular signaling is not mediated via known PARs. It may, however, involve proteolytic cleavage of a yet unknown member of the PAR family (181-183). Thus, TF initiated signaling can occur in an autocrine or paracrine manner. Autocrine signaling occurs, when TF-FVIIa mediated signals are independent of activation of coagulation and restricted to the TF expressing cell. Paracrine signaling is possible when proteases distal from FVIIa are formed, these being able to diffuse and act on neighboring cells.

TF-dependent Signaling with FVIIa and the Cytoplasmic Domain of TF

The TF-dependent metastatic potential in melanoma and CHO cells is substantially reduced when they are transfected with truncated cDNA of TF lacking its cytoplasmic domain (136, 165), implying that the TF cytoplasmic domain is actively involved in TF mediated metastasis. The cytoplasmic domain of TF contains three serine residues which can potentially serve as acceptor sites for phosphorylation (184, 185). Serine residues 253 and 258 have been demonstrated to be phosphorylated by protein kinase C (PKC) (184, 186), PKC is activated by increased levels of intracellular calcium (187), and PKC inhibitors typically reduce TF expression (184, 186, 188). Therefore, it is supposed that phosphorylation of the cytoplasmic region might confer FVIIa initiated intracellular signaling. However, it is not yet known how the phosphorylation signal is transmitted to the TF cytoplasmic domain (109, 136, 165) and which other protein kinases may also be involved.

The cytoplasmic domain-dependent signaling observed in the pro-metastatic function of TF is independent from protease-mediated MAP kinase activation, since neither FVIIa nor FXa significantly activate MAP kinase activity in TF transfected CHO cells (109) and deletion of the cytoplasmic domain does not affect FVIIa dependent MAP kinase activation (178). It remains to be studied how FVIIa triggers signals resulting in TF-phosphorylation and whether some tumor cells are phosphorylating TF endogenously, while others do not, potentially explaining some of the diverging results presented above. Furthermore, the role of phosphorylation in the interaction of TF with cytoskeletal proteins has yet to be studied.

TF-dependent Signaling with the Cytoplasmic Domain of TF

In some tumor cells, effects of TF are independent of exogenous ligands and proteolytic signaling. Studies in Meth-A sarcoma and melanoma cell lines demonstrate that overexpression of TF induces tumor growth and angiogenesis, even in the presence of the anticoagulant warfarin or the thrombin inhibitor hirudin (122). Although it is not yet known whether these tumor cells secrete another TF ligand or whether tumor cells overexpressing TF are capable to mediate TF dependent signaling in the absence of a ligand (121, 122), these data indicate that TF may induce signaling through its cytoplasmic domain. Furthermore, transfection of melanoma cell lines, characterized as low

TF- and low VEGF producers. With several mutated forms of TF demonstrated that cytoplasmic tail deletion resulted in a significant reduction of VEGF expression, while TF synthesis by the tumor cells was not altered (121). In contrast, a procoagulant defective TF mutant maintained its VEGF inducing ability in this model. Consistently, neither FVIIa, FFR-ck-VIIa nor hirudin affected VEGF expression (121). Furthermore, incubation of tumor cells with an excess of anti-TF antibodies (blocking its procoagulant activity) or anti-VEGF antibodies, abolishing VEGF dependent TF induction, also failed to inhibit VEGF expression (97). Therefore, the cytoplasmic tail of TF seems to be essential and sufficient to induce VEGF in some melanoma cell lines (121). Preliminary data indicate that the MAP kinase pathway is involved in this cytoplasmic signaling as the MAP kinase inhibitor PD98059, but not PKC inhibitors such as staurosporin abolished VEGF induction in melanoma cell lines overexpressing TF (P. Nawroth, unpublished observation). It is not yet known, whether the MAP kinase phosphorylates the TF cytoplasmic tail or whether it is involved in a signal distant from TF through an as yet unidentified TF triggered signal. TF requires correct anchorage into the membrane, which can be supported by neutral or negatively charged phospholipids (189, 190) and appears to be a necessary prerequisite for TF function. In view of these observations, it was a surprise when Watanabe and coworkers (191) demonstrated that soluble TF added into a diffusion chamber induced angiogenesis in cultured endothelial cells. The effect was inhibited by anti-TF antibodies and also by FII, FVII and FIX, and hence was independent of the coagulation pathway (191). This implies that dimerization of TF could be a potential mechanism of mediating and/or enhancing angiogenesis in the presence of soluble TF. This hypothesis may also explain some of the differences in TF dependent VEGF induction observed in several studies.

Conclusion

An increasing number of studies demonstrate that TF may participate in angiogenesis, vascularisation and tumor metastasis. Data derived from clinical studies (indicating only a correlation but not a causative role) and data of genetically engineered tumor cells provide evidence in some models that TF is, indeed, involved in several different aspects of tumor cell biology. However, the exact mechanism is not yet understood. Future studies looking not only at the regulation of TF expression but also at the regulation of its phosphorylation and signal transduction are required.

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